Chapter 9
Modification of the Host Epigenome by Parasitic Protists

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Abstract Protozoan parasites compose a large group of ubiquitous unicellular eukaryotic organisms that closely interact with, and frequently reside within, a larger host. These parasitic protists rely on their host for nutrients, energy, and biomaterials. The host–parasite interaction is complex, as parasites strive to achieve a delicate balance of survival and replication without inducing host death. The host, in turn, tries to protect itself by various means including activation of death pathways in order to limit parasite spread. Therefore, successful parasites have developed highly evolved tactics in order to avoid host immune recognition and intracellular killing and subvert the host to their needs. To this end, various mechanisms of hijacking of host processes via parasite-derived or secreted effectors have been described. It has recently come to light that parasites also induce alterations to the host epigenomic landscape. Changes in host DNA methylation, histone posttranslational modifications, nucleosome positioning, chromatin assembly, and regulation of transcription have been noted in the parasitized host. To date, only a few parasite-derived effectors have been shown to directly modify host chromatin, and it remains to be elucidated whether parasite-induced alterations to the host epigenomic landscape are brought on specifically by parasites or are due to the host response. Finally, while various parasites target different components of host epigenomic landscape, common themes in subversion of host pathways and process emerge. We aim to review what is known about parasite modulation of host epigenome and touch on some conserved themes in this host–parasite interplay.

Keywords Parasite • Protist • Host • Epigenome • Noncoding RNA • Chromatin remodeling • Histone • DNA methylation • *Toxoplasma gondii* • Theileria • Leishmania • Plasmodium • Cryptosporidium • Microsporidia • Eimeria

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9.1 General Comments

9.1.1 Overview of Pathogenic Protists

Protozoan parasites are a vast group of distinct unicellular eukaryotic organisms, capable of infecting humans, animals, and insects, with unique and complex life cycles. Considering the enormous diversity of these organisms, we will limit discussion below to include examples of protozoans able to cause disease in humans and animals. Many of these parasites reside and replicate inside host cells for at least part of their life, inducing significant changes in cellular processes including the epigenetic landscape. Individual parasites have distinct interactions with the host. Some such as *Leishmania* spp. and *Theileria* inhabit the cytoplasm, while others such as *Toxoplasma gondii* form and reside in a parasitophorous vacuole. *Theileria,* in particular, which targets mainly cattle, live within the host cytoplasm of leukocytes and utilize the host cell division apparatus, inducing continuous proliferation and immortalization of the host cells (Spooner et al. 1989), while *Leishmania* species, obligate intracellular parasites targeting macrophages of mammals, reside within host-derived phagolysosomal vacuoles that are adapted to avoid and subvert host immune defenses (Lievin-Le Moal and Loiseau 2015). Some organisms, such as *T. gondii,* possess a highly evolved armament of effectors that are translocated across the parasitophorous vacuole and specifically target host processes (Boothroyd and Dubremetz 2008; Fentress and Sibley 2011). Parasites induce vast changes in host transcription, as has been demonstrated during infection with *T. gondii* (Blader et al. 2001; Chaussabel et al. 2003; Jia et al. 2013), *Plasmodium*-infected hepatocytes (Albuquerque et al. 2009; Chattopadhyay et al. 2011; Kaushansky et al. 2013), and most recently host cells of the avian malaria parasites (Videvall et al. 2015). These infections affect pathways involved in metabolism, cell death, differentiation, and cell cycle (Albuquerque et al. 2009). Despite major life cycle differences, parasites commonly exploit the close association with their mammalian host to achieve defense of self and subversion of the host.

In addition to invasion and replication, protozoan parasites have evolved an array of strategies to evade the host immune system and promote survival. Extensive remodeling of host cell subcellular structure is a feature of many host–parasite interactions. These include incorporating parasite protein into the cell membrane, restructuring the host cytoskeleton, sequestering mitochondria, and altering subcellular localization of organelles, forming transvesicular networks and constructing new organelles (Silmon de Monerri and Kim 2014). *T. gondii*, as an example, reorganizes host ER and mitochondria, relocalizing them to the parasitophorous vacuole (Sinai et al. 1997), and has also evolved to alter host metabolism and subvert energy and metabolic machinery to its cause (Wiley et al. 2010; Menendez et al. 2015). Along with these structural and metabolic changes to the host cell, reprogramming of the host cell transcriptome following infection or exposure is well documented for a significant number of infectious

organisms. Distinct transcriptional changes occur in host cells following infection or exposure, in a pathogen-specific manner, and these changes may be long-lasting or transient (Chaussabel et al. 2003). Studies have additionally demonstrated that the host transcriptome may be differentially altered depending on the life cycle stage of the pathogen (Fouts and Boothroyd 2007). Together, these studies suggest that observed transcriptional effects are unique to the specific host–pathogen interaction. Importantly, while many changes in host gene expression are organism specific, overall there appears to be conservation of host pathways targeted by pathogens during infection.

9.1.2 Overview of Host Epigenetic Landscape

Eukaryotic genomes are folded into highly controlled chromatin complexes composed of well-organized hierarchical structures of DNA wound around histone-containing nucleosome complexes. Chromatin composed of nucleosomes then further folds into secondary and tertiary structures to allow efficient and ordered DNA packaging (Luger et al. 2012). The specific confirmation of chromatin renders DNA open and accessible (euchromatin) or tightly compacted and inaccessible (heterochromatin) for transcription factor and RNA polymerase binding. Changes that occur in the structure of chromatin are considered to be "epigenetic," i.e., not encoded in the DNA, and include both short- and long-term alterations to chromatin without change to the underlying DNA sequence. Traditionally, there are considered to be three main types of epigenetic regulation, which include DNA methylation, histone posttranslational modifications, and noncoding RNAs, initially described in the context of cell differentiation (Spivakov and Fisher 2007) (Fig. 9.1).

The best-studied mechanism of epigenetic modification that arises on the DNA itself is methylation. DNA methylation plays a role in regulation of gene expression and is typically associated with transcriptional repression, though recent studies implicate hydroxymethylation in transcriptional activation (Ito et al. 2010). Methylation events occur either de novo or as part of genome maintenance by replicating the methylation pattern of the complementary strand. In eukaryotes, cytosine bases are methylated by DNA methyl transferase (DNMT) enzymes. In mammalian genomes, DNA methylation mainly occurs on CpG dinucleotides, which are often located in CpG-rich regions known as CpG islands (CGI), frequently found at transcriptional start sites. Methylated nucleotides can be further converted from 5-methylcytosine to 5-hydroxymethylcytosine by a family of TET (Ten-eleven translocation) enzymes resulting in hydroxymethylation. Hydroxymethylation was initially thought of as a step towards demethylation, although hydroxymethylation itself has been implicated in stem cell differentiation (Dawlaty et al. 2014). Methylation of promoter regions silences genes by blocking transcription initiation, while methylation in gene bodies may facilitate elongation and block abnormal transcriptional initiation (Jjingo et al. 2012). Additionally, DNA methylation is thought to play a role in splicing, and methylation at centromeres may be

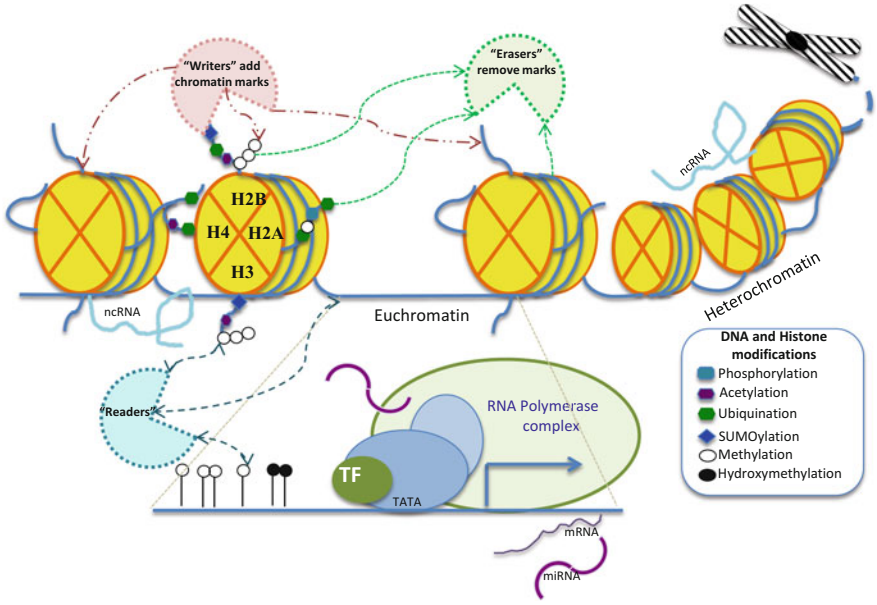

Fig. 9.1 Overview of host epigenetic landscape. Schematic representation of DNA and nucleosome complexes. The host epigenetic landscape is shaped by modifications including histone PTMs, DNA methylation, chromatin remodeling, and ncRNAs, including miRNAs. These modifications are applied by groups of enzymes referred to as "Writers" and "Erasers," where "Writers" add chromatin and histone marks (HAT, HMT, DNMT, kinases), while "Erasers" remove those marks (HDAC, HDM, NuRD, phosphatase). Combinations of specific marks afford precise regulation of DNA accessibility and transcriptional regulation, as they are recognized by "Readers"—specific transcription factors and polymerase machinery. Abbreviations: *PTM* post-translational modifications, *ncRNA* noncoding RNA, *mRNA* messenger RNA, *miRNA* microRNA, *HDAC* histone deacetylase, *DNMT* DNA methyl transferase, *HAT* histone acetyl transferase, *HMT* histone methyl transferase, *HDM* histone demethylase, *NuRD* Nucleosome remodeling deacetylase; Lollipop symbols represent methylation (*white*) and hydroxymethylation (*black*)

involved in overall chromosomal stability. This pattern of genome methylation, while inherited and more stable at CGIs, also undergoes changes during development and aging especially when occurring at the non-CGI regions (Jones 2012). A number of excellent reviews on the function and mechanism of DNA methylation are available (Ndlovu et al. 2011; Pelizzola and Ecker 2011; Jjingo et al. 2012; Jones 2012; Pastor et al. 2013; Dawlaty et al. 2014).

While DNA methylation is generally associated with gene silencing, posttranslational modification (PTM) of histones (or "chromatin marks") can either activate or repress transcription. Nucleosomes form basic structural units of chromatin, and DNA packaging into nucleosomes is essential for controlling DNA accessibility. Each nucleosome is an octamer composed of dimers of H2A, H2B, H3, and H4 histone proteins. Histones, particularly their N-terminal tails, are subject to complex posttranslational modifications, which collectively serve to recruit other proteins to chromatin in order to mediate changes in transcription (Strahl and Allis 2000). Among the histone modifications that have been described are

phosphorylation, methylation, acetylation, ubiquitylation, and SUMOylation. These modifications are tightly choreographed as different modifications can target the same residues in a competitive manner. Chromatin marks are applied or removed by specific enzymes commonly referred to as "writers" [histone acetyltransferases (HAT), histone methyltransferases (HMT), kinases] or "erasers" [histone deacetylases (HDAC), histone demethylases (HDM), phosphatases]. Erasers and writers tightly regulate the binding affinity of histones to DNA and further control organization of nucleosome complexes. Specific combinations of PTMs on nucleosomes allow specificity for DNA interactions with and recognition by other protein complexes, and nucleosomes themselves serve as platforms for further regulation or chromatin access by "readers" and chromatin modifiers, including ncRNAs, which together form a multiprotein macromolecular complex (Jenuwein and Allis 2001). In addition, particular PTMs are associated with specific locations within the genome and serve as a foundation for readers by recruiting additional structural and regulatory assemblies. For example, H3K4me3 is found predominantly in promoters of active genes and plays a role in recruitment of the transcriptional machinery being recognized by plant homeodomain (PHD) finger domain-containing proteins (Chi et al. 2010), while H3K27me3 is enriched at promoters of repressed genes and together with CGI methylation marks gene silencing. Misregulation of these specific modifications has been shown to play a role in cancer (Chi et al. 2010). The total combination of histone PTMs alters the affinity of histones for DNA, and modulation of histone–DNA interactions regulates DNA winding and therefore the accessibility of DNA to transcription factors.

In addition to modifications of histones and nucleotides directly, the accessibility of DNA and position of nucleosomes is altered by transcription factors, their associated complexes such as RNA polymerase, as well as the Polycomb complex, which, when bound to the DNA targets, interfere with binding of histones and other transcriptional regulatory proteins. This chromatin remodeling also modulates histone nucleosome positioning and movement along the DNA, causing destabilization, reassembly, and eviction of nucleosomes (Struhl and Segal 2013). It should be noted that the ordering of such events is not clear, as nucleosomes mediate recruitment of other machinery, which in turn may prevent nucleosome binding.

A newly emerging arena in the study of epigenetics is evaluation of functions of noncoding RNAs (ncRNAs). The ncRNAs play a major role in posttranscriptional regulation and genome maintenance and are involved in a wide range of regulatory processes including DNA methylation, histone PTMs, DNA silencing, formation of the molecular scaffolding necessary for chromatin structure and stability, and posttranscriptional regulation of mRNAs (Joh et al. 2014; Fitzgerald and Caffrey 2014; Scaria and Pasha 2012). Additionally, antisense transcripts may play a role in coordinating chromatin and histone marks by recruiting DNMT or histone-modifying enzymes (Faghihi and Wahlestedt 2009). The ncRNAs can be long or small, and small ncRNAs are further divided into microRNA (miRNA), small interfering RNA (siRNA), and PIWI interacting RNA (piRNA). MicroRNAs (miRNAs) are small noncoding ssRNAs ~20–25 nucleotides in length that are best known for regulation of posttranscriptional mRNA processing and play a key role in mRNA and gene expression, while long noncoding RNAs (lncRNA) are

>200 nucleotides in size and interact with mRNAs, miRNAs, and RNA-binding proteins (RBP) to further regulate protein expression. Significant adjustment of protein expression occurs at the level of mRNA by miRNAs, RNA-binding proteins, and lncRNAs, and regulation at the level of mRNA allows for specific and rapid alteration of protein levels. These posttranscriptional modifications mediated by ncRNAs fine-tune regulation of mRNA stability and translation, especially for genes involved in immune and inflammatory responses, such as IFN gamma. RNA-specific regulation of components of immune response and inflammation has been studied in great detail, and readers are referred to excellent reviews on the roles of noncoding RNA in immune regulation (Fitzgerald and Caffrey 2014; Schwerk and Savan 2015).

All of these tightly orchestrated arrangements of DNA methylation, histone PTMs, nucleosome positioning, and other types of chromatin remodeling form a precise signature for regulation of transcription and are targeted by pathogens for their purpose. Reshaping of the host epigenome is an emerging mechanism of host modulation exploited by a variety of pathogens (Silmon de Monerri and Kim 2014; Cheeseman and Weitzman 2015). Unlike viruses, protozoa and bacteria do not insert DNA into the host genome and so have evolved different strategies to influence chromatin and gene regulation. In bacteria, secreted proteins known as nucleomodulins target host chromatin and transcription, altering downstream signaling pathways. Nucleomodulins such as AnkA from *Anaplasma* spp. directly target host DNA and recruit host chromatin and histone-modifying enzymes (HDAC) to globally alter host chromatin (Bierne et al. 2012; Sinclair et al. 2014). Intracellular parasitic protists, similar to intracellular bacteria and viruses, reside within the host cell either within some type of parasitophorous vacuole (*T. gondii*) or free in the host cytoplasm, thus avoiding direct recognition by antibodies and cells of immune system. Parasites then interface with their host via parasite-derived effector proteins, which can be secreted in a targeted manner (e.g., *T. gondii* ROP or GRA proteins) or delivered via exosomes. In turn, parasites utilize host nutrients, metabolites, and energy sources that can be transported or diffuse into the parasite's niche. However, intracellular parasites are subjected to other host defenses including host apoptosis and have devised ways of scavenging or subverting nutrient and energy pathways, while avoiding host defenses and preventing host demise. This review focuses on the epigenetic changes and chromatin remodeling that occur in the host cell following infection or exposure, and various mechanisms used by protozoan parasites to hijack the host transcriptome (Fig. 9.2 and Table 9.1). Additionally, we explore common themes in the host processes that are targeted and postulate biological implications of these alterations.

9.2 Alteration of DNA Methylation

Parasitic protists have evolved mechanisms of modulating host chromatin state by either amending host cytosine methylation or by modifying enzymes that bring about these modifications. Expressly, *Leishmania, Plasmodium*, and *T. gondii*

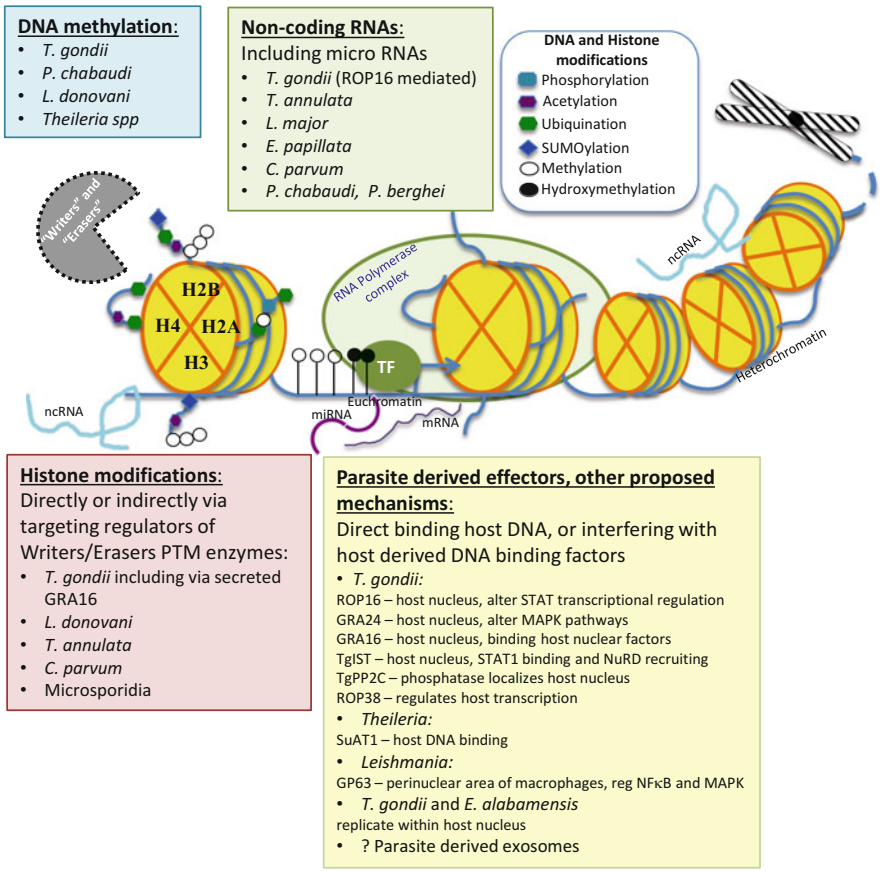

Fig. 9.2 Host epigenetic machinery targeted by parasites. Parasites induce specific alterations to the host epigenome by targeting key mechanisms of landscape design, including regulation of DNA methylation, regulation of enzymes responsible for PTMs, and interfering with chromatin accessibility and nucleosome positioning. Details of mechanisms and references are provided in the text

parasites have been shown to induce explicit changes in host DNA methylation. In a study evaluating methylation changes in macrophages infected with *L. donovani*, Marr et al. found diffuse changes in methylation at CGI in promoters as well as gene bodies (Marr et al. 2014). They noted significant changes in regions involved in regulation of key pathways of host response including NFkB, JAK/STAT, MAPK, mTOR, chemokine signaling, and others (Marr et al. 2014; Arango Duque and Descoteaux 2015). Similarly, genome-wide analysis of methylation of host promoters during infection of mice with *P. chabaudi* notes changes in the methylation of promoters of a number of genes, including toll-like receptor genes (Al-Quraishy et al. 2013). Finally, studies have focused on evaluating link between host behavior and infection, and a recent study implicates *T. gondii*-induced changes in DNA methylation as the cause for change in behavior of infected rats (Hari Dass and Vyas 2014). In response to *T. gondii* infection, hypomethylation of the arginine

Table 9.1 Select parasites and their effect on the host epigenome

Parasite (effector)	Specific host target	Biologic effect	Reference
DNA methylation			
L. donovani	Multiple, HDAC4	CpG islands, gene promoters, and gene bodies	Marr et al. (2014)
P. chabaudi		Change in promoter methylation	Al-Quraishy et al. (2013)
T. gondii	Arginine vasopressin promoter	Increased production arginine vasopressin—may be link to behavioral change	Hari Dass and Vyas (2014)
T. gondii		Global increase in DNA methylation in testes	Dvorakova-Hortova et al. (2014)
T. gondii	E3 Ubiquitin Ligase UHRF1	Downregulation of DNA methyltransferase I leading to increased H3 phosphorylation and host cell cycle arrest	Brunet et al. (2008), Unoki et al. (2009)
Theileria spp.	Casein kinase 2 (CK2) →DNMT	Phosphorylates DNA methyl transferase DNMT3	Dessauge et al. (2005b)
Histone and chromatin remodeling			
T. gondii	Histone H3 PTMs	Decreased H3S10 phosphorylation and H3 acetylation, specifically at IL10 and TNF promoters	Leng et al. (2009), Leng and Denkers (2009)
T. gondii (TgIST)	Chromatin remodeling	STAT regulation regions	Lang et al. (2012), Olias et al. (2016), Gay et al. (2016)
T. gondii	Histone acetylation	Alterations in histone and nuclear protein lysine acetylation	Bouchut et al. (2015)
T. gondii	UHRF1 E3 ubiquitin ligase → Phospho H3	Downregulation of UHRF1, associated with accumulation of phosphorylated H3 associated with mitosis and cyclin expression	Brunet et al. (2008), Unoki et al. (2009)
T. gondii (GRA 16)	Nuclear PP2A phosphatase, HAUSP deubiquitinase	Alter histone ubiquitin PTM of histone	Bougdour et al. (2013)
L. donovani	HDAC4 methylation	Alteration in HDAC4 gene body and upregulation of expression	Marr et al. (2014)
T. annulata	SMYD3 methyltransferase	Induced expression of SMYD3 methylates H3 histone	Cock-Rada et al. (2012)
T. annulata	HDAC9 downregulation		Kinnaird et al. (2013)

(continued)

Table 9.1 (continued)

Parasite (effector)	Specific host target	Biologic effect	Reference
T. annulata	PARP family	DNA binding, modifying DNA-binding proteins, CTCF, and histones, alteration in DNA methylation	Kinnaird et al. (2013)
C. parvum	? HDAC	Alterations in CX3CL1 chemokine controlled by HDAC	Zhou et al. (2013)
Microsporidia Nosema ceranae	Histones H3-like, H4 expression	Expression changes in histones in honeybee midgut epithelium	Aufauvre et al. (2014)
Noncoding RNA			
T. gondii	Alterations in miRNA profile, miR-132	Alteration in host miRNA in brains of infected humans and mice	Thirugnanam et al. (2013), Xu et al. (2013), Xiao et al. (2014), Li et al. (2015)
T. gondii (ROP16)	miR-146a, miR-155	Upregulated in brains of infected mice	Cannella et al. (2014)
T. gondii	miR-17-92, miR-106b-25	Altered expression in human macrophages and fibroblasts	Zeiner et al. (2010), Cai et al. (2013, 2014)
T. annulata	miR-155	Upregulated in transformed leukocytes	Marsolier et al. (2013)
C. parvum	miR-424, miR-503, miR-98, let-7	Changes in host miRNA profile in infected cholangiocytes	Zhou et al. (2009), Chen et al. (2007), Hu et al. (2009, 2010)
E. papillata	miRNA profile	Upregulated in mouse intestinal epithelia	Dkhil et al. (2011)
L. major	miRNA profile	Significant alteration in host miRNAs	Lemaire et al. (2013)
P. chabaudi	miRNA profile	Alteration in host hepatocyte miRNAs	Delic et al. (2011)
P. berghei	miRNA profile	Alteration in mosquito vector miRNAs	Biryukova et al. (2014)

DNMT DNA Methyltransferase, *HDAC* histone deacetylase, *PARP* Poly-ADP ribose polymerase, *PTM* posttranslational modification

vasopressin promoter was observed, which was implicated in increased production of vasopressin in the medial amygdala region of the brain, the region that perceives fear. Specifically, rats infected with *T. gondii* show a reduced aversion to cats, instead demonstrating attraction (Berdoy et al. 2000). Changes in behavior patterns and changes in the brain have been described in rats (Flegr and Markos 2014; Hari Dass and Vyas 2014; Vyas 2015), and this phenomenon may also affect humans as *T. gondii*-infected men perceive the smell of cat urine as being more pleasant as compared to uninfected males (Flegr et al. 2011). Infection with *T. gondii* not only alters behavior but also dramatically reduces reproductive fitness in mice (Dvorakova-Hortova et al. 2014). Specifically, *T. gondii* infection was associated with increased testicular global DNA methylation, as well as increased DNA methylation of genes involved in spermatogenesis (Dvorakova-Hortova et al.

2014). It is interesting to note that in the context of alteration in methylation and behavior, mice infected with *T. gondii* also have decreased levels of serum testosterone (Kankova et al. 2011), especially since regulation of vasopressin expression in medial amygdala by promoter CPG methylation was shown to be regulated by testosterone (Auger et al. 2011). Overall, these studies explore *T. gondii*-induced changes in host DNA methylation and propose specific physiologic consequences to the host. In an alternative approach, *Theileria* parasites appear to utilize an indirect method of altering host DNA methylation by targeting DNMTs. In a study examining how *Theileria* spp. manipulate signaling, it was found that parasites induce constitutive activation of casein kinase 2 (CK2) (Dessauge et al. 2005b). CK2 has numerous roles in transcriptional regulation, including regulating DNA methylation by phosphorylating DNA methyltransferase DNMT3 (Deplus et al. 2014) as well as playing a role in PI3-K activation and the MEK/ERK and Akt/PKB pathways (Dessauge et al. 2005b). By inducing CK2 and regulating DNMT3, *Theileria* induce alteration of the host DNA methylation landscape. It should be noted that apart from *Theileria*-induced CK2, the mechanisms underlying parasite-induced changes in host DNA methylation are largely unknown. Nevertheless, these data suggest that protozoan parasites have evolved to regulate host processes to alter genome methylation patterns that modify function of key cellular processes, including signaling pathways, behavior, and reproduction.

9.3 Histone Modification and Chromatin Remodeling

Parasites have evolved mechanisms to specifically induce epigenetic changes in the host histone code. These include alteration of host histone PTMs either directly or by regulating enzymes that impact these modifications, and alteration of expression of individual histones including variants histones that may differ in DNA-binding affinity (Siggens and Ekwall 2014). A handful of studies have attempted to elucidate host epigenetic changes in response to *T. gondii* infection. In an evaluation of macrophages following infection with *T. gondii,* there was notable impairment of histone 3 (H3) phosphorylation (at Serine 10 residue) and H3 acetylation at the IL10 and TNFα promoters (Leng et al. 2009; Leng and Denkers 2009), as well as impairment of chromatin remodeling at STAT1-regulatory regions (Lang et al. 2012). There was additional interference with chromatin remodeling at the TNF-alpha promoter preventing binding of RNA polymerase transcriptional machinery (Leng et al. 2009). Recent work demonstrated that *T. gondii* secreted factor TgIST (*T. gondii* inhibitor of STAT1 transcriptional activity) translocates to the host cell nucleus where it directly interacts with STAT1 protein promoting its nuclear sequestration, as well as associates with Mi-2/NuRD (nucleosome remodeling deacetylase complex) to facilitate chromatin remodeling and inhibition of transcription (Olias et al. 2016; Gay et al. 2016). In a study focused specifically on evaluating changes in lysine acetylation in cortical astrocytes infected with *T. gondii,* changes were noted in lysine acetylation of nuclear proteins including proteins that function in chromatin biology including histones, as well as proteins involved in

RNA processing and transcription (Bouchut et al. 2015). Specifically, data demonstrated more than twofold increase in acetylation of core histones including histone H3, H4, H2A.Z, among others, while other members of histone cluster and histone-like proteins demonstrated greater then twofold decrease in acetylation (Bouchut et al. 2015). Since histone acetylation is associated with transcriptional regulation, specifically activation (Berger 2007), such substantial alteration in host histone acetylation following parasite infection implies active modulation of the host epigenome, though the exact mechanism is not yet known. Additional work demonstrated that infection by *T. gondii* leads to downregulation of the host UHRF1 E3 ubiquitin ligase gene, accompanied by accumulation of phosphorylated histone H3, a mitotic histone mark, and reduction of host cell cyclin levels (Brunet et al. 2008; Unoki et al. 2009). *T. gondii* also subverts host transcription via GRA16, which travels to the nucleus and forms a complex with host PP2A phosphatase and HAUSP deubiquitinase (Bougdour et al. 2013), which are known to sway ubiquitin PTM balance on nuclear proteins including histones (Khoronenkova et al. 2011; Bougdour et al. 2014). Thus, *T. gondii* specifically targets host nuclear proteins and PTM machinery to promote remodeling of the epigenome.

Other intracellular parasites have also been shown to influence host histones. In *L. donovani*-infected macrophages, analysis of host DNA methylation revealed significant alteration in the methylation of the HDAC4 gene body associated with upregulation of HDAC4 expression (Marr et al. 2014). In an alternative example, *Nosema ceranae*—a member of *Microsporidia,* a diverse group of ~200 genera of obligate intracellular pathogens that infect a wide range of animals, fish, and insects, induce increased expression of histone H3-like and histone H4 in midgut epithelia of honeybees (Aufauvre et al. 2014; Calderon et al. 2015). *Cryptosporidium parvum* is another Apicomplexan parasite that primarily invades mucosal surfaces. Study of host epithelial immune regulation following infection with *C. parvum* revealed alteration in CX3CL1 chemokine that is at least in part directed by HDAC (Zhou et al. 2013). Finally, *Theileria*-transformed leukocytes demonstrate upregulation of matrix metalloproteinase (MMP-9), which is important in cancer cell migration and metastases. This *mmp9* regulation is in part achieved by inducing expression of SMYD3 methyltransferase in infected leukocytes, which methylates histone H3 (H3K4me3) at the *mmp9* promoter leading to transcriptional activation (Cock-Rada et al. 2012). Additionally, an expression microarray of lymphosarcoma cells infected with *T. annulata* revealed significant downregulation in HDAC9 expression (Kinnaird et al. 2013). Together, emerging data assert that various parasites have evolved mechanisms of specifically targeting host chromatin structure and assembly by targeting histone expression and posttranslational modifications.

9.4 Noncoding RNAs

Considering the key role for ncRNAs in regulation of host processes, it is not surprising that pathogens have evolved to target ncRNAs. Viruses widely utilize lncRNA and miRNA for transcriptional regulation to subvert host metabolic

pathways (Scaria and Pasha 2012). Specifically, Kaposi's Sarcoma Herpesvirus (KHSV) encodes a miRNA that alters host cell metabolism in part by downregulating EGLN2 and HSPA9, components of the mitochondrial import machinery, which induce a glycolytic shift in host metabolism via stabilization of HIF1a—a master regulator of oxygen sensing and metabolism (Yogev et al. 2014). Evidence is now emerging that other pathogens including parasites modulate similar pathways during host cell infection. Unlike viruses, however, parasites are not known to secrete ncRNA but instead are hypothesized to modulate host-derived miRNAs by regulating their expression (Hakimi and Cannella 2011), as well as RNA PTMs such as methylation, further confounding complexity of host epigenetic regulation (Joh et al. 2014).

Infections with a number of parasites have been shown to alter host ncRNAs. A handful of investigations have evaluated alterations in host ncRNA specifically miRNA in the brain during *T. gondii* infection. In a study of human brain cancers, *T. gondii* infection was shown to alter host miRNA to facilitate carcinogenesis (Thirugnanam et al. 2013), while a microarray analysis of host neuroepithelioma cells infected with different strains of *T. gondii* revealed strain-specific alteration in host transcription (Xiao et al. 2011). Similarly, analysis of mouse brains after infection with *T. gondii* revealed a subset of nine host miRNAs that appear to be explicitly induced by infection (Xu et al. 2013). One of these differentially expressed ncRNAs is miR-132. Mammalian miR-132 is involved in regulation of neuronal synapses and plays a key role in a number of neurologic and psychiatric disorders including schizophrenia, depression, and Parkinson's disease, and it is therefore intriguing that miR-132 is targeted by *T. gondii* (Bicker et al. 2014). Interestingly, change in expression of miR-132 was different depending on the chronicity of infection. During acute infection, there was upregulation of miR-132, thought to contribute to modulation of dopamine signaling in brains of infected mice (Xiao et al. 2014), while there was significant downregulation of miR-132 in brains of chronically infected mice (Li et al. 2015). In addition to miR-132, host miR-146a and miR-155 were also strongly upregulated in brains of mice during chronic infection with *T. gondii,* in ROP16-dependent manner (Cannella et al. 2014). miR-146 is known to dampen the TLR4 response via NFκB-dependent TRAF6 and IRAK1, and miR-155 modules TLR signaling (Schwerk and Savan 2015). Furthermore, miR-155 belongs to the oncomiR group of cancer-associated microRNAs, which have been shown associated with malignant cells, with miR-155 specifically associated with cMyc overexpression (Esquela-Kerscher and Slack 2006). Similar to *T. gondii*, *Theileria* parasites also induce expression of host miR-155 (Marsolier et al. 2013; Cannella et al. 2014). In *Theileria*-transformed leukocytes, there is upregulation of miR-155 regulated by cJun and AP1 transcription factors, which in turn was shown to repress expression of DET1 important in cJun ubiquitination and stabilization (Marsolier et al. 2013).

In addition to changes noted in neuronal cells, *T. gondii* has also been shown to alter the expression of host microRNAs during infection of human fibroblast cells, especially miR-17-92 and miR-106b-25, both oncomiRs important in regulating cell cycle and apoptosis (Zeiner et al. 2010). Similarly, miRNA profiling of

T. gondii-infected human macrophages revealed several host miRNAs important in apoptosis, including miR-17-92, whose expression is altered in a STAT3-regulated manner (Cai et al. 2013, 2014). Likewise, miRNA expression profiling of *C. parvum*-infected cholangiocytes (bile duct epithelial cells) revealed broad alterations in the host miRNA profile (Zhou et al. 2009). Specifically, there was notable suppression of transcription of host miRNAs (miR-424 and miR-503) mediated by hijacking histone deacetylases and NFkB signaling pathways (Zhou et al. 2013). Additionally, infection of human cholangiocytes with *C. parvum* led to alteration in host expression of miR-98 and let-7 miRNA oncomiRs (Chen et al. 2007; Hu et al. 2009, 2010). Other parasites have also induced changes in host epigenomic landscape via modulation of miRNAs. miRNA microarray analysis revealed upregulation of a number of mouse intestinal epithelial cell miRNAs during infection with coccidian *Eimeria papillata* (Dkhil et al. 2011), while analysis of miRNA expression in *L. major*-infected human macrophages revealed downregulation of 64 of 365 miRNAs, especially those involved in BCL, p53, NFκB, TLR, and HIF1α signaling pathways (Lemaire et al. 2013). Further studies are needed to tease out whether these shifts in host miRNA profile favor parasite virulence or host defense.

Several studies have examined the role of ncRNAs during *Plasmodium* infection. *Plasmodium* parasites have complex interplay with their hosts, inducing alterations in the host miRNA profile, as well as themselves being subject to host miRNA regulation (Cohen et al. 2015). In a mouse model of malaria, specific changes in mouse hepatocyte miRNA expression during *P. chabaudi* infection have been elucidated (Delic et al. 2011). Analysis of mouse hepatocytes after infection with *P. chabaudi* induced upregulation of 3 and downregulation of 16 distinct miRNAs, and this pattern was similar both during primary infection and reinfection, suggesting that a distinct set of host miRNAs are involved in the response to infection (Delic et al. 2011). A study evaluating the miRNA profile of the infected mosquito vector likewise found alterations in levels of distinct miRNAs in response to blood meal with *P. berghei* (Biryukova et al. 2014). While the precise mechanism that *Plasmodium* parasites utilize to induce these miRNA changes is unknown, such changes in host ncRNA landscape must afford some advantage to either the parasite or the host.

In addition to modulation of host ncRNAs, there is a suggestion that parasites themselves may encode ncRNAs that target host processes. Some parasites in fact possess small RNA processing machinery and small RNA repertoires (Braun et al. 2010). Sacar et al. conducted a computational analysis of *T. gondii* RNAs and noted mammalian like hairpin structures, which they hypothesized could be delivered to the host to modulate host transcription (Sacar et al. 2014). The actual role of these hairpins in pathogenesis and parasite–host interplay is unknown. Thus, parasites have evolved mechanisms to perturb host ncRNAs, especially microRNA regulatory pathways that control the immune and inflammatory response to infection. These examples demonstrate that parasites target key host pathways including those involved in immune response, by affecting host ncRNA specifically miRNAs.

9.5 Protozoan Effectors Reshape the Host Epigenome

Epigenetic changes in the host during infection may be due to a direct effect by parasite-derived factors or an indirect effect where parasites target host regulators of the epigenetic landscape to induce the observed changes. Some parasite-derived factors influence the host cell by acting on genome and regulatory pathways through cytoplasmic signaling without entering the nucleus, while a number effectors have been shown to participate in reshaping of the host epigenetic landscape by directly interacting with host DNA and transcription (analogous to bacterial nucleomodulins). Additionally, pathogen-derived effectors can closely resemble host factors, a mechanism known as molecular mimicry that has recently been reviewed (Aliberti et al. 2003; Via et al. 2015). Similar to bacterial pathogens, parasites encode proteins that target the host epigenome (Cheeseman and Weitzman 2015). Although some of these proteins target to the host nucleus, only a few are known to directly interact with host chromatin. In a characteristic example, *Theileria* parasites encode AT hook DNA-binding proteins TashA and SuAT1. SuAT1, which contains a nuclear localization motif, is found in the nucleus of infected host cells and participates in control of cell cycle as well as functions to alter host cell morphology (Swan et al. 2001, 2003; Shiels et al. 2004). *T. gondii* parasites secrete a large number of dense granule (GRA) and rhoptry (ROP) proteins into the host cell. These target host cell processes in the cytoplasm, nucleus, and other subcellular compartments and induce dramatic changes in subcellular morphology, signaling, and transcriptional remodeling (Boothroyd and Dubremetz 2008; English et al. 2015; Hakimi and Bougdour 2015). Specifically, *T. gondii* GRA24 localizes to the host nucleus, where it augments host MAPK signaling by inducing autophosphorylation of p38a MAPK, inducing alteration in Erg and cFos transcription (Braun et al. 2013; Bougdour et al. 2014). It should be noted that the GRA24 kinase interacting motif closely mimics those of host p38, ERK, and JNK factors. Similarly, GRA16 mediates host transcriptional dysregulation by directly binding host nuclear factors and altering the activity of PP2A and HAUSP to induce HAUSP-dependent degradation of p53, an important transcriptional regulator of cell cycle (Bougdour et al. 2013). Another parasite-secreted factor, GRA15, participates in activation of the host NFκB pathway (Rosowski et al. 2011; Hakimi and Bougdour 2015). Secreted kinase ROP16 localizes to the host nucleus where it activates STAT3 and STAT6 transcription leading to restriction of host cell growth (Saeij et al. 2007; Butcher et al. 2011). In addition, ROP16 is responsible for a large number of transcriptional changes and inhibition of cytokine signaling. Recently identified TgIST protein also localizes to host nucleus where it interacts with both STAT1 and NuRD complex, mediating transcriptional repression (Olias et al. 2016; Gay et al. 2016). Another rhoptry protein, *T. gondii* TgPP2C, is a protein phosphatase that is targeted to the host nucleus, and while its exact function is not yet known, parasites knocked out for this gene exhibit mild growth defect (Gilbert et al. 2007). Finally, *T. gondii* ROP38 downregulates host transcription, especially MAPK, STAT, and Fos signaling pathways (Peixoto et al. 2010). Similarly,

Leishmania GP63 metalloprotease, which regulates host NFκB/AP1 and MAPK signaling, localizes to a perinuclear area of host macrophages (Isnard et al. 2015), where it may contribute to changes in host transcription (Arango Duque and Descoteaux 2015; Isnard et al. 2015).

Although intracellular parasites possess a number of effectors that modulate the host epigenome, the molecular mechanisms for parasite-induced changes in the host epigenetic landscape remain unknown. An emerging area of great interest in host–pathogen interactions is centered on discovery of parasite-derived extracellular vesicles that appear to be similar to eukaryotic exosomes used for cell–cell communication. Parasite-derived exosomes that may target the host have been described for *Leishmania*, *Trichomonas, Trypanosomes*, and *Plasmodium* parasites (Mantel and Marti 2014; Coakley et al. 2015; Schorey et al. 2015). For example, *Leishmania*-derived GP63 and EF1α are found in parasite-derived exosomes (Silverman et al. 2010; Silverman and Reiner 2011), and *Trichomonas vaginalis* extracellular parasites secrete exosome-like vesicles containing proteins and RNA that modulate host response and adhesion (Twu et al. 2013). Furthermore, RNA transfer has been shown to be mediated via exosomes during cell–cell communication, and recent studies of nematodes have demonstrated transfer of small RNAs in the parasite-derived exosomes (Coakley et al. 2015). It would, therefore, be intriguing to ponder whether parasites utilize exosomal ncRNA transfer to modulate their host, especially since *Leishmania*-derived exosomes have been shown to harbor conserved ncRNAs (Lambertz et al. 2015).

In addition to secretion of specific host-targeted effectors, several parasites have been observed to replicate inside host nuclei. Actively dividing *T. gondii* were observed in the nucleus of various cell types, where they appear to develop in the absence of a vacuolar membrane (Azab et al. 1973; Barbosa et al. 2005). *Eimeria alabamensis*, a related Apicomplexan, have also been observed inside nuclei of intestinal villi (Nishida et al. 2009). Similarly, some microsporidia undergo intranuclear replication (Palenzuela et al. 2014). The biological significance of these observations is unknown, but may represent alternative pathways for parasites to develop and potentially influence the host nucleus.

9.6 Commonly Targeted Pathways

While various parasites employ distinct mechanisms for reshaping epigenomes, targeting of key canonical pathways has emerged as a common theme in the host–parasite interaction. As one would predict, these pathways are highly conserved and are involved in immune modulation, cell cycle progression, metabolism, and overall cell signaling, specifically including regulation by Jak/STAT, NFκB, MAPK pathways, IFN-gamma signaling, and HIF1α. Some of these mechanisms have recently been reviewed (Luder et al. 2009; Melo et al. 2011; Cheeseman and Weitzman 2015; Hakimi and Bougdour 2015; Luder et al. 2015). While a number of alterations to pathways occur in the host cell cytoplasm via protein modification,

we will focus on specific epigenetic mechanisms, involving targeted alteration to chromatin structure, including subversion of transcription. While different pathogens target many of the same host pathways, typically each has a unique mechanism. Some parasites induce upregulation of a target protein, while others sequester inhibitors or target stabilization mechanisms. HIF1a and NFkB pathways are often perturbed as detailed below. There is significant cross talk between signaling pathways that together tightly orchestrate control of the cell. We present a brief overview linking examples of parasite alterations to the host epigenome with manipulation of major host pathways (Fig. 9.3).

Mitogen-activated protein kinases (MAPK) are a large family of serine/threonine kinases that transmit extracellular signals via a cytoplasmic signal transduction pathway to modulate essential cellular processes including apoptosis, stress response, and survival. One of the final steps in the pathway involves phosphorylation and activation of Erk kinase, JNK kinase, or p38, which, as dimers, translocate into the nucleus to regulate transcription of genes involved in stress response, apoptosis, and inflammation. MAPK also phosphorylate and regulate other transcription factors including cFos, cMyc, STAT3, and p53 to regulate apoptosis (Yang et al. 2013; Dhillon et al. 2007). Downstream factors of the MAPK cascade participate in shaping of the host epigenome, as specifically cJun interacts with the nucleosome remodeling complex (Aguilera et al. 2011). Considering the key role of MAPK signaling in cellular processes and responses to various stimuli, it is not surprising that parasites have evolved strategies to modulate and subvert this signal transduction pathway. At least one of the mechanisms by which parasites achieve these regulatory changes is alteration in host DNA methylation as shown to occur specifically at MAPK pathway targets for *L. donovani* (Marr et al. 2014), as well as targeted by CK2 kinase activated by *Theilera* (Dessauge et al. 2005b). *T. gondii* GRA24 specifically binds and promotes activation of MAPK/p38 causing nuclear translocation and phosphorylation of its targets including cytokines involved in inflammatory response, overall creating a proinflammatory state (Braun et al. 2013), while ROP38 kinase causes downregulation of transcription of the MAPK pathways (Peixoto et al. 2010). These molecules illustrate how the balance of *T. gondii* parasite factors can modulate the host MAPK pathway. *Theileria* parasites also modulate MAPK signaling, and cells infected and transformed by *Theileria* demonstrate constitutive activation of JNK and AP1 transcription factor (Chaussepied et al. 1998; Lizundia et al. 2007; Hayashida et al. 2010). cFos and cJun are ubiquitous transcription factors downstream of MAPK/MEK pathways, involved in regulation of a wide range of essential cellular processes. Both families contain several proteins, and cFos and cJun transcription factors combine to form an Activator Protein 1 (AP1) transcription factor, which binds DNA. Recent work has specifically shown that *Theileria* parasites secrete a peptidyl-prolyl isomerase (PIN1) homologue into the host cell that causes cJun stabilization via degradation of host ubiquitin ligase FBW7, leading to oncogenic transformation of the host cell (Marsolier et al. 2015). *Leishmania* parasites induce cleavage of the cJun component of the AP1 transcription factor via parasite-derived GP63 protein (Contreras et al. 2010). Finally, *L. Mexicana* alters dendritic cell signaling leading to

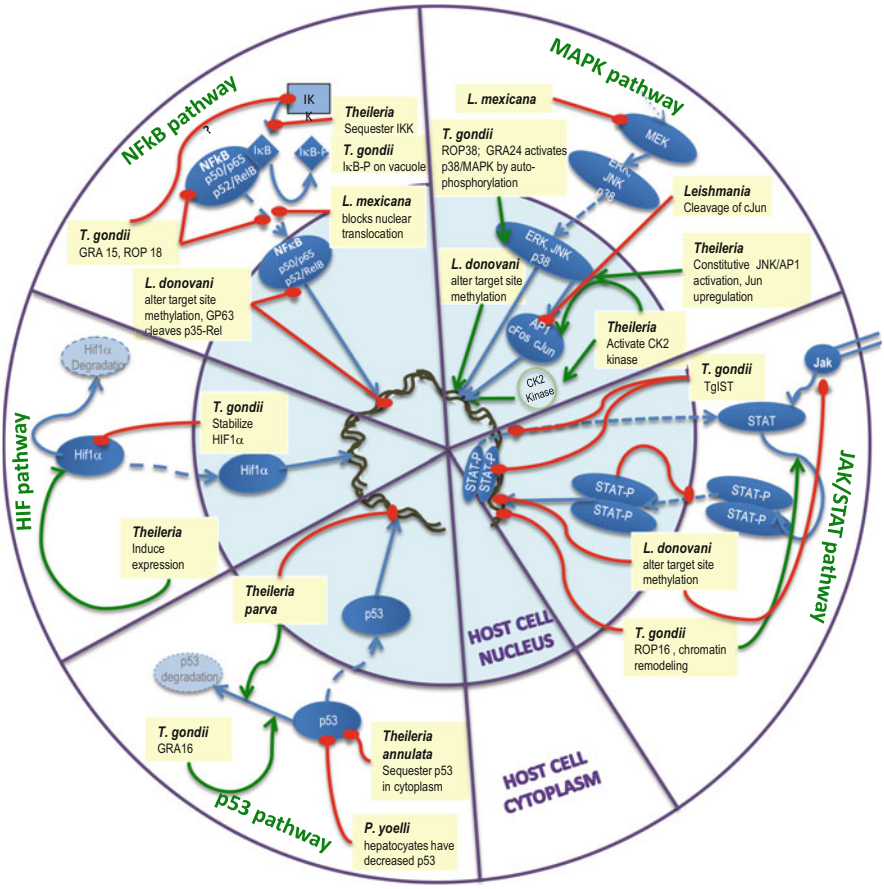

Fig. 9.3 Host regulatory pathways targeted by parasitic infection. Parasites alter the host epigenome by manipulating transcriptional regulators of key host processes involved in immune response, cell cycle, death pathways, metabolism, and other signal transduction events. Shown is a cartoon schematic of select pathways and how they are targeted by parasites. Parasites target host NFkB, p53, and MAPK transcriptional regulation in part to subvert host cell death and cytokine response pathways. Additionally, parasites subvert host metabolism as regulated by the HIF1 pathway. Details and references are described in the text. Red connectors denote inhibition; green arrows represent activation

inactivation of host MAPK and inhibition of phosphorylation of downstream p38 and ERK (Contreras et al. 2014). These signal transduction changes eventually lead to epigenomic remodeling, as direct interactions of downstream MAPK proteins with histone modifications and chromatin remodeling have been described, providing a mechanistic link between signal transduction cascade and chromatin remodeling (Aguilera et al.) Thus, while utilizing very different mechanisms, distinct parasites target the MAPK pathway to control host processes and the epigenetic landscape.

Nuclear Factor Kappa-light-chain-enhancer of activated B cells (NFκB) is a family of transcription factors including NFκB (p50 and p52) and Rel members that are key transcriptional regulators of cytokines such as IL12 and IFNγ as well as growth factors and anti-apoptotic factors. NFκB is found in the cytoplasm in an inactive complex with an inhibitor protein, IκB. During cell surface receptor activation, there is cytoplasmic recruitment of IκB kinase (IKK) that inactivates IκB and allows NFκB to translocate into the nucleus and induce transcription (or silencing) of target genes (Gilmore 2006). Parasites have evolved means of hijacking NFκB to regulate transcription to promote evasion of the host immune defense and resistance to apoptosis. *T. gondii* subverts NFκB activation using GRA15 and ROP18 secreted proteins (Rosowski et al. 2011). Specifically, ROP18 associates with the dimerization domain of NFκB p65, promoting its degradation (Du et al. 2014), while GRA15 interferes with nuclear translocation of NFκB and NFκB-mediated transcription of target genes (Rosowski et al. 2011). Similarly, the NFκB pathway is a key host target for *Theileria*, though it is manipulated using a different mechanism involving IKK. IKK accumulates on *Theileria* schizont surface and causes degradation of pathway inhibitors, allowing NFκB translocation into the nucleus and binding target genes (Heussler et al. 2002). A possible mechanism for sequestration of IKK involves TpSCOP (*T. parva* schizont-derived cytoskeleton-binding protein), which induces resistance to apoptosis (Hayashida et al. 2010). Although prior work demonstrated modulation of NFκB via phosphorylation and accumulation of IkB on the surface of the *T. gondii* parasitophorous vacuole as well, the effect on the signaling pathway is not well defined (Molestina et al. 2003; Sinai et al. 2004; Molestina and Sinai 2005a, b). Analysis of miRNA in *C. parvum*-infected cholangiocytes revealed that some of the differentially expressed miRNAs have NFkB-binding sites in their promoters, suggesting a mechanism for their regulation (Zhou et al. 2009, 2013). Additionally, as already noted, methylation changes induced by *L. donovani* in macrophages occur in the NFkB pathway (Marr et al. 2014), while GP63 cleaves the p35-RelA subunit of NFkB (Gregory et al. 2008), presumably to alter host NFκB regulated transcription. In an alternate mechanism, *L. mexicana* prevents nuclear translocation of AP1 and NFκB components in infected dendritic cells (Contreras et al. 2014). Finally, microarray analysis of lymphosarcoma cells infected with *T. annulata* revealed significant alteration in a number of key transcriptional regulators, including AP1 subunits FOS and JUN, as well as NFκB, all of which were activated during infection (Kinnaird et al. 2013). Alterations in key host processes implicated in cell growth, cytokine signaling, cell division, motility, and death were also observed. Studies in cancer cells established that JNK and NFκB signaling play opposite roles and together impose a tightly regulated balance in transcription. By altering either NFκB or MAPK/JNK signaling, parasites shift host cell fate to promote their survival.

p53 is an important tumor suppressor protein and transcription factor involved in regulation of apoptosis, cell cycle, and DNA repair. It is also subject to extensive posttranslational modifications including phosphorylation, ubiquitination, acetylation, and methylation (Kruse and Gu 2009). Considering its cornerstone role, p53 is

another major parasite target. As mentioned, *T. gondii* modulates host p53 by targeted degradation via GRA16 with PP2A phosphatase and HAUSP deubiquitinase (Bougdour et al. 2013). In a remarkable example of hijacking of host apoptosis, *T. annulata* causes immortalization of host leukocytes, in part by targeting p53 (Haller et al. 2010). Contrary to *T. gondii*, *Theileria* inactivates p53 protein by sequestering it in the cytoplasm on the schizont membrane, preventing its translocation into the nucleus. Curing cells of *Theileria* infection by drug treatment results in p53 translocation to the nucleus (Haller et al. 2010). Additionally, *Theileria parva*-transformed leukocytes upregulate MDM2, a major regulator of p53. MDM2 binding blocks p53 transcriptional activity and promotes p53 ubiquitination and degradation, such that there is an overall decrease in p53 (Hayashida et al. 2013). Similarly, hepatocyte-infected *Plasmodium yoelii* parasites have decreased levels of p53 (Kaushansky et al. 2013). Akin to p53, parasites target the transcription factor cMyc, a central controller of a large number of genes involved in cell cycle, apoptosis, differentiation, and metabolism. Significant host upregulation and stabilization of cMyc occurs during infection with *T. gondii*, possibly in a JNK-mediated manner (Franco et al. 2014). Similarly, cMyc is stabilized by phosphorylation by CK2 in *Theileria*-transformed leukocytes, promoting anti-apoptotic signaling (Dessauge et al. 2005a). Overall, data suggest that parasites modulate the host epigenome by secreting specialized effectors or sequestering and hijacking key transcriptional regulators of cell cycle and apoptosis, effectively disabling transcription of pro-apoptotic factors to ensure their own survival.

Janus kinase–signal transducer and activator of transcription (JAK-STAT) pathway transmits extracellular messaging from cytokines and IFNγ bound to cell receptors directly into transcriptional regulation by binding to promoters of target genes involved in growth and immune response. STAT proteins are located in the cytoplasm and are inactive until they are recruited to an activated receptor, become phosphorylated by an associated JAK kinase, dimerize (either homo- or heterodimers of different STAT proteins), and translocate to the nucleus where they bind to specific IFNγ activation sequences, thus causing transcription (or repression) of the target gene (Aaronson and Horvath 2002). Similar to p53, STAT proteins can undergo phosphorylation by other regulatory proteins, including MAPK kinases, which can alter the efficiency of STAT–DNA interactions. Host IFN gamma (IFNg) signaling is one of the main mechanisms utilized in resistance and elimination of invading parasites, and protozoan parasites have evolved mechanisms to avoid IFNg-directed death (Suzuki et al. 1988; Yarovinsky 2014; Luder et al. 2015). *T. gondii* hijack host signaling cascades to make host cells unresponsive to IFNγ, by interfering with STAT signaling and its DNA binding to IFNγ response elements. Specifically, *T. gondii* induces alteration in the host epigenetic landscape leading to impairment of histone acetylation at IFNγ regulated promoters and improper assembly of chromatin regulatory machinery at the IFN-γ-targeted STAT1 response elements (Kim et al. 2007; Lang et al. 2012; Rosowski and Saeij 2012). Additionally, early studies of genetic crosses demonstrated that *T. gondii* specifically targets STAT pathways in the infected host cell (Saeij et al.

2007). Secreted *T. gondii* protein Rop16 localizes to the host nucleus and subverts host signaling machinery by directly phosphorylating STAT3 and STAT6 proteins, leading to restriction of host cell growth and a number of other transcriptional changes (Saeij et al. 2007; Ong et al. 2010; Butcher et al. 2011; Denkers et al. 2012). In addition, Rop16 phosphorylates STAT1, rendering it inactive and therefore subverting the host cell IFNγ response (Rosowski and Saeij 2012). In eukaryotic cells, transcriptionally active regions are marked by histone H3 and H4 lysine acetylation at the N-terminal tails, important for assembly of transcriptional apparatus. However, macrophages infected with *T. gondii* do not exhibit acetylation of lysine residues in histones of IFNγ-responsive promoters while use of HDAC (deacetylase) inhibitor restored the IFNγ response (Lang et al. 2012). Recent studies aiming to identify the mechanism utilized by *T. gondii* to inhibit STAT1/IFNg signaling noted another regulatory mechanism involving removal of STAT1 from the nuclear-cytoplasmic cycling pool by maintaining it as chromatin bound and preventing disassociation of STAT1 from DNA (Rosowski et al. 2014). Recently identified TgIST appears to be involved in this STAT1 chromatin binding as well as *T. gondii* related transcriptional repression (Olias et al. 2016; Gay et al. 2016). In a different tactic, evaluation of mouse dendritic cells infected with *T. gondii* revealed phosphorylation and nuclear translocation of STAT1 without binding to IFN response elements. This STAT1 rearrangement was induced by parasite invasion but not dependent on parasite replication (Schneider et al. 2013). All together, these mechanisms provide a clue as to how *T. gondii* subvert host IFNγ response via epigenetic and transcriptional dysregulation of STAT signaling, thus promoting parasite survival and growth. Targeting of STAT signaling is utilized by other parasites as well; e.g., *Leishmania* alter DNA methylation of infected macrophages at CpG islands, specifically disrupting JAK/STAT and MAPK signaling (Marr et al. 2014). Furthermore, *L. donovani* infection of macrophages also induced inhibition of JAK/STAT signaling, in part by SHP-1 phosphatase-induced blockade of Jak phosphorylation, as well as induced reduction of Interferon Regulatory factor 1 (IRF1), suggesting parasite-induced impairment in STATa nuclear translocation (Olivier et al. 2005; Matte and Descoteaux 2010).

Intracellular parasites rely on the host cell for their nutritional needs and therefore cause shifts in overall host metabolism. Hypoxia-inducible factor-1 (HIF1) is a master regulator of transcription in response to changes in host oxygen, iron, and glucose availability. The stability of the HIF1-alpha (HIF1α) subunit is tightly regulated in the cytoplasm, such that alteration in overall host state attenuates HIF1a degradation and allows HIF1 (α + β heterodimer) to translocate to the nucleus where it binds to HREs (hypoxia response elements). HREs regulate transcription of genes involved in metabolism and glucose utilization. HIF1α itself is further regulated by posttranslational modifications. Early microarray analyses revealed significant alterations in the expression of genes involved in host metabolism in response to *T. gondii* infection, and it was subsequently shown that parasites alter HIF function by modulating its expression and stability, presumably to subvert host metabolic processes and key metabolite targeting (Blader et al. 2001; Wiley et al. 2010; Singh et al. 2012; Medjkane et al. 2014; Menendez et al.

2015; Metheni et al. 2015). In *Theileria*-infected and transformed leukocytes, there is a notable shift in host metabolism towards glycolysis, known as the Warburg effect or aerobic glycolysis. This is largely controlled by HIF1, which in turn is regulated by NFκB and AP-1 that are also altered during infection (Metheni et al. 2015). Along with the STAT and JUN pathways, HIF1α is specifically targeted and stabilized during *T. gondii* infection (Spear et al. 2006; Wiley et al. 2010). In a similar manner, *Leishmania* parasites alter HIF1 function by upregulating HIF1 expression and stabilization of HIF1 against degradation (Singh et al. 2012). MicroRNA-210 (hypoxamir) is a major hypoxia-inducible miRNA, whose expression is regulated by HIF1α, which plays a role in modulating mitochondrial respiration and alteration in cell proliferation (Chan et al. 2012). Expression of miR-210 was significantly increased during human macrophage infection with *L. major* parasites, and its upregulation in macrophages was dependent on HIF1α (Lemaire et al. 2013). Whether these alterations in host metabolism are a result of direct parasite targeting or whether they are fundamental to the host response to infection remains to be elucidated. The dysregulation of host metabolic state allows redirecting of nutrients, energy, and metabolic intermediates to promote parasite growth. It is also worth noting that alpha ketoglutarate (αKG) is a key intermediate of the mitochondrial TCA cycle and is a cofactor for a large number of enzymes involved in essential host processes, including TET enzymes that regulate DNA CpG methylation, JMDM1 JmjC histone demethylases (Tsukada et al. 2006), and PHD2 enzyme (prolyl hydroxylase domain 2) which is directly involved in HIF1α stability (Semenza 2007). Other work in cancer biology also links metabolic intermediates directly to changes in epigenome (Moussaieff et al. 2015). Therefore, by altering host cell metabolism and inducing a shift away from mitochondrial respiration, parasites cause reduction in available αKG, potentially altering host cell processes that directly regulate DNA methylation and the epigenetic landscape.

Parasites regulate a number of other key host processes including cell death pathways such as apoptosis and cell cycle progression. Gene expression and signaling are at the heart of cell cycle progression. Perturbation of cell cycle checkpoints and regulation of apoptosis are used by intracellular parasites to ensure their survival. Intracellular parasites are protected from immune recognition, and the infected cell may undergo apoptosis to curb infection. Intracellular parasitic protists including *Toxoplasma*, *Leishmania*, *Theileria*, and *Cryptosporidia* inhibit apoptosis of the infected host cell (Heussler et al. 2001). Cells infected with *T. gondii* are resistant to extracellular induction of apoptosis (Nash et al. 1998). Additionally, *T. gondii* parasites appear to actively interfere with host death pathways. During infection, *T. gondii* modulates genes involved in apoptotic pathways, primarily NFκB signaling. Degradation of pro-apoptotic BCL2 proteins altered miRNA and STAT (STAT3, miR17-92, and Bim) signaling, and degradation of pro-apoptotic p53 also contributes to inhibition of apoptosis, promoting host cell and parasite survival (Carmen and Sinai 2011; Cai et al. 2014). *Theileria* and *Cryptosporidium* similarly stabilize the host NFκB pathway to abrogate apoptosis

(Heussler et al. 2001). In an analogous manner, there is a notable decrease in pro-apoptotic p53 in *P. yoelii*-infected hepatocytes, supporting cell survival (Kaushansky et al. 2013). While utilizing similar mechanisms in inhibition of apoptosis, these parasites induce distinct effects upon the host cell cycle. *T. gondii* induces arrest in the host cell cycle by downregulating expression of UHRF1 E3 ubiquitin ligase, as well as by manipulating ERK kinase, leading to induction of G1/S phase progression and blockage in G2/M transition (Brunet et al. 2008; Molestina et al. 2008; Unoki et al. 2009). *Leishmania* parasites induce host cell cycle arrest at an earlier stage, during G0 to S transition, via downregulation of cyclin-dependent kinases and upregulation of cyclin kinase inhibitors p21 and p27 (Kuzmenok et al. 2005). *Theileria* parasites reside directly in the host cytoplasm of leukocytes and coopt the host cell division apparatus to induce continuous uncontrolled proliferation and oncogenic transformation of the host cells, coupling host cell division to parasite division (Spooner et al. 1989). *Theileria* subvert host cell cycling mainly by activation of the NFκB pathway, but microarray analysis of infected cells revealed changes in mRNA levels of a significant proportion of host genes, underscoring the complexity of host–parasite interactions (Shiels et al. 2006; Durrani et al. 2012; Kinnaird et al. 2013). Intracellular parasites commonly actively target and modulate host cell cycle and apoptosis pathways to facilitate parasite survival and replication. Overall, intracellular parasites have developed sophisticated mechanisms for targeting and subverting key host processes involved in chromatin assembly and structure, significantly altering the host epigenomic landscape.

9.7 Concluding Remarks

Protozoan parasites have a complex relationship with their hosts, relying on them for nutrients and metabolic products, while avoiding host immune defenses and preventing their demise. To that effect, various pathogens including viruses, bacteria, and eukaryotic parasite utilize similar means of subverting their host. The host–pathogen interaction has been studied extensively, and through recent work it has become apparent that significant alterations occur in the host epigenetic landscape during infection. Some of these changes are achieved by specific secretion of protozoan proteins into the host, which may alter host epigenetics directly by modulating chromatin packaging and transcription of specific genes, or indirectly by modifying activity of vital host proteins or host miRNA. Furthermore, while there are global changes to the overall epigenomic landscape of the host, a number of regulatory alterations occur in regions encoding conserved elements of essential cell processes such as cell signaling, death pathways, metabolism, and growth. Additionally, alteration in availability and function of key host transcription factors further tempers the host epigenetic landscape. In this context, it is apparent that by disturbing regulation of the signaling cascades, parasites induce perturbations in the host epigenome.

The term "host" has been used here to describe any cell infected by a parasite, but in fact, notable and distinct changes to the epigenome occur in a wide range of infected organisms from mammals to insect vectors and in a wide range of cell types including cells of the immune system, intestinal epithelia, and neurons. It is intriguing that epigenetic changes have been described in cells that are not directly infected, suggesting a significant role for cell–cell communication in disease pathogenesis. Subversion of immune cells may promote parasite dissemination and survival. Moreover, changes to the host epigenome can be transient or long term, as seen in *Theileria*-cured leukocytes (Kinnaird et al. 2013). It is intriguing to speculate exactly what role long-term alteration, especially those occurring in the immune cells, may play in cellular memory and cell-mediated immunity, and whether these changes are further inherited and become part of "epigenetic memory." Finally, while some of the host changes are due to a direct parasite effect, others should be attributed to the host response to the infection. This concept has been described for *T. gondii* infection wherein three general groups of genes or processes are modulated—those necessary for parasite survival or "pro-parasite," those necessary for host defense or "pro-host," and "bystander" genes that do not appear to be directly necessary for either (Blader et al. 2001; Blader and Saeij 2009).

Our understanding of the mechanisms for how pathogens reshape the host epigenetic landscape is still rudimentary. It will be interesting to see whether pathogens induce unique or universal epigenetic signatures of infection on the host that can be used in clinical diagnoses and treatment. There clearly is an intricately laced regulatory web modulating host epigenetic landscape, and further work is needed to dissect the exact mechanisms and causal interrelationships.

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